The Examiner asserted that the specification lacks deposit information for the cA2 antibody on which the instant method claims depend.

In response, applicants respectfully traverse the Examiner's rejection.

The Court of Appeals for the Federal Circuit has stated that:

> No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988).

The Examiner notes that the subject application, at page 8, lines 15-23, incorporates by reference information on cA2 to other U.S. patent applications not listed as priority documents. In particular, the subject application incorporates by reference information on cA2 described in U.S. Application No. 08/192,093 (filed February 4, 1994) (now U.S. Patent No. 6,284,471), U.S. Application No. 08/192,102 (filed February 4, 1994) (now U.S. Patent No. 5,656,272), U.S. Application No. 08/192,861 (filed February 4, 1994) (now U.S. Patent No. 5,919,452), U.S. Application No. 08/324,799 (filed October 18, 1994) (now U.S. Patent No. 5,698,195) and Le, et al., International Publication No. WO 92/16553 (published October 1, 1992).

The referenced U.S. patent applications disclose the cloning and recombinant expression of the cA2 monoclonal antibody, including the sequencing of the light and heavy chain variable regions. The referenced patent applications also provide significant description of the properties (e.g. glycosylation, epitopic specificity and affinity) of the chimeric anti-TNFα antibody cA2. With this information, screening of antibodies which have the same or similar properties is straightforward to one skilled in the art.

Thus, given the guidance presented in the referenced patent applications, it would be a routine matter for one skilled in the art to produce the monoclonal antibody cA2 and antibodies chemically and structurally similar to the cA2 antibody for use in the claimed invention. Therefore, the cA2 antibody is enabled by the present specification, in view of the incorporation by reference to these referenced applications, and a deposit is not required.

In view of the above remarks, applicants maintain that claims 14, 15, 36 and 37 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 14, 15, 36 and 37 under 35 U.S.C. §112, second paragraph, as being allegedly indefinite for failing to point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner asserted that claims 14, 15, 36 and 37 are vague and indefinite in the recitation of cA2 as the only means of identifying the monoclonal antibody on which the claims depend.

In response, applicants respectfully traverse the Examiner's rejection.

As stated in the applicants' specification (see, e.g., page 12, lines 12-17), chimeric monoclonal antibody cA2 has been defined and described in detail in, for example, U.S. Application No. 08/192,102 (now U.S. Patent No. 5,656,272). This reference provides significant description of the properties and methods for producing chimeric monoclonal antibody cA2, thereby clearly establishing that the characteristics of cA2 are known and that the term clearly defines an antibody whose features are well defined. There is nothing impermissible in employing a laboratory designation in a claim.

In view of the above remarks, applicants maintain that claims 14, 15, 36 and 37 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Rejections Under 35 U.S.C. §103(a)

The Examiner rejected claims 6, 8, 29 and 30 under 35 U.S.C. §103(a) as allegedly unpatentable over Wakefield, et al. (Arteriosclerosis, Thrombosis and Vascular Biology, 1995, Vol. 15, pages 258-268), in view of Arbustini, et al. (American Journal of Cardiology, 1991, Vol. 68, pages 36B-50B), as evidenced by the abstract of Riipi, et al. (Infection and

Immunity, 1990, Vol. 58, pages 2750-2754).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest every element of the claims. Second, one of ordinary skill must have been motivated to combine the teachings of the cited references at the time of the invention. Third, there must have been a reasonable expectation that the claimed invention would succeed.

To support a *prima facie* case of obviousness, Wakefield, et al., Arbustini, et al. and Riipi, et al., combined, would have to teach or suggest every element of the claims, which they do not do. Moreover, these references, when combined, would have to provide a reasonable expectation of success.

Claims 6, 8, 29 and 30 are discussed above. Briefly, these claims provide methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject *diagnosed as suffering from thrombosis*.

Wakefield, et al. teach that anti-TNF antibodies partially reduce vein wall neutrophil extravasation, and thus partially inhibit the vein wall inflammatory response which occurs as a

result of venous thrombosis. Wakefield, et al. suggest that a decrease in the vein wall inflammatory response may result in a decline in the manifestations of chronic venous insufficiency, a syndrome which occurs *after* venous thrombosis. However, Wakefield, et al. do not teach the treatment or prevention of thrombosis, or decreasing plasma fibrinogen, itself. They also do not teach methods for treating a subject diagnosed as suffering from thrombosis.

Arbustini, et al. do not cure these defects. Arbustini, et al. teach that TNF has been immunohistochemically detected in smooth muscle cells, endothelial cells and macrophages of human femoral, coronary and carotid atherosclerotic arteries, and therefore, may play a role in the evolution of disease (i.e., atherosclerosis).

However, Arbustini, et al. also teach that TNFα was found in lipid-rich plaques *either with or without thrombus*. Furthermore, Arbustini, et al. state that "interestingly, like inflammatory infiltrates *and TNFα*, IL-2 is present in plaques with large amounts of pultaceous core *not strictly related to thrombosis* but rather to the plaque composition" (see page 49B).

Like Wakefield, et al., Arbustini, et al. do *not* teach or suggest methods of treating or preventing thrombosis, or decreasing plasma fibrinogen.

The abstract of Riipi, et al. also does not cure the deficiencies of Wakefield, et al. and Arbustini, et al. Riipi, et al. teach that pre-administration of anti-mouse-TNFα,

polyclonal antibodies in mice results in the inhibition of the increase of plasma fibrinogen that occurs upon challenge with *Candida albicans* or mouse TNFα.

First, Riipi, et al. do not teach or suggest methods of *treating or preventing thrombosis* at all. Second, Riipi, et al. do not teach or suggest methods of decreasing plasma fibrinogen in a subject *diagnosed as suffering from thrombosis*. In fact, nowhere do Riipi, et al. even mention the term "thrombosis."

In light of these teachings and their shortcomings, the Examiner has failed to show that the cited references teach or suggest every element of the claims, or create a motive to combine or expectation of success. To maintain otherwise would be hindsight.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 29 and 30 over Wakefield, et al., Arbustini, et al. and Riipi, et al.

The Examiner also rejected claims 6, 8-10, 12-15, 29-32 and 34-37 under 35 U.S.C. §103(a) as allegedly unpatentable over Wakefield, et al., in view of Arbustini, et al. and the abstract of Riipi, et al., and further in view of Le, et al. (U.S. Patent No. 5,656,272).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To support a *prima facie* case of obviousness, Wakefield, et al., Arbustini, et al. and Riipi, et al., combined with Le, et al., would have to teach or suggest every element of the claims, which they do not do. Moreover, these references, when combined, would have to provide a reasonable expectation of success.

Claims 6, 8-10, 12-15, 29-32 and 34-37 provide methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject *diagnosed as suffering from thrombosis*. In one embodiment of the invention, the TNF antagonist is an anti-TNF antibody. In another, the antibody is the chimeric monoclonal anti-TNF antibody cA2.

Wakefield, et al., Arbustini, et al. and Riipi, et al. are discussed above. Again, these references combined do not teach or suggest methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject diagnosed as suffering from thrombosis.

Le, et al. fail to cure the deficiencies of Wakefield, et al., Arbustini, et al. and Riipi, et al. Instead, Le, et al. teach methods of treating TNFα-mediated pathologies and conditions generally with anti-TNFα antibodies, including cA2.

Le, et al. do not teach the treatment or prevention of thrombosis, or of increased plasma fibrinogen, in a subject diagnosed as suffering therefrom. Le, et al., do not include thrombosis or plasma fibrinogen in their exhaustive list of TNFα-mediated pathologies and conditions, nor do they even mention the terms "thrombosis" or "plasma fibrinogen." Therefore, Le, et al., in combination with the other cited references, do not provide an impetus for using this antibody method in connection with a method of the type claimed.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8-10, 12-15, 29-32 and 34-37 over Wakefield, et al., in view of Arbustini, et al. and the abstract of Riipi, et al., and further in view of Le, et al.

The Examiner also rejected claims 6, 8, 29 and 30 under 35 U.S.C. §103(a) as allegedly unpatentable over Wakefield, et al., in view of Arbustini, et al., as evidenced by the abstract of Riipi, et al., and further in view of Esser (WO 92/09203).

In response to the Examiner's rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To support a *prima facie* case of obviousness, Wakefield, et al., Arbustini, et al. and Riipi, et al., combined with Esser, et al., would have to teach or suggest every element of the claims, which they do not do. Moreover, these references, when combined, would have to provide a reasonable expectation of success.

Briefly, claims 6, 8, 29 and 30 provide methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject *diagnosed as suffering from thrombosis*.

Wakefield, et al., Arbustini, et al. and Riipi, et al. are discussed above. Again, these references combined do not teach or suggest methods of treating or preventing thrombosis, or decreasing plasma fibrinogen, comprising administering a therapeutically effective amount of a tumor necrosis factor antagonist to a subject diagnosed as suffering from thrombosis.

Esser fails to cure the deficiencies of Wakefield, et al., Arbustini, et al. and Riipi, et al. Esser teaches essentially what Le, et al. teach, i.e., general methods of treating TNF-mediated diseases with TNF inhibitors.

Esser does not teach the treatment or prevention of thrombosis, or of increased plasma fibrinogen, in a subject diagnosed as suffering therefrom. Although Esser theorizes that since TNF has pro-inflammatory activities, its early production, i.e., during the initial stages of an inflammatory event, make it a likely mediator of tissue injury in disorders such as myocardial infarction, Esser does not recite thrombosis or plasma fibrinogen as TNFα-mediated diseases, nor does it even mention the terms "thrombosis" or "plasma fibrinogen."

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 6, 8, 29 and 30 over Wakefield, et al., in view of Arbustini, et al., as evidenced by the abstract of Riipi, et al., and further in view of Esser.

In view of the above remarks, applicants maintain that claims 6, 8-10, 12-15, 29-32 and 34-37 satisfy the requirements of 35 U.S.C. §103(a).

Obviousness-Type Double Patenting

The Examiner provisionally rejected claims 6, 8-10, 12-15, 29-32 and 34-37 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-15 of co-pending Application No. 09/598,079, claims 1-23 of co-pending Application No. 09/754,004, claims 32-54 of co-pending Application No. 09/921,937 and claims 1-20 of co-pending Application No. 10/252,489, all in view of Wakefield, et al. and Arbustini, et al., as evidenced by the abstract of Riipi, et al.

In response, applicants respectfully traverse the Examiner's provisional rejection, and maintain that, in view of the above remarks, the Examiner has not properly set forth grounds for this provisional rejection.

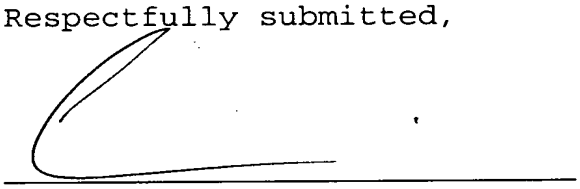
Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection be reconsidered and withdrawn and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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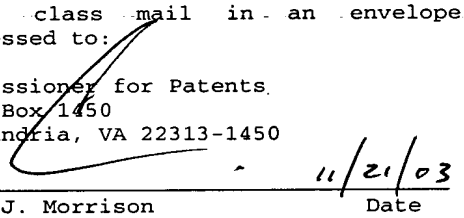

11/21/03

Alan J. Morrison Date
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